Missense Variants in ATM in 26,101 Breast Cancer Cases and 29,842 Controls

Abstract:
Background: Truncating mutations in ATM have been shown to increase the risk of breast cancer but the effect of missense variants remains contentious. Methods: We have genotyped five polymorphic (minor allele frequency, 0.9-2.6%) missense single nucleotide polymorphisms
(SNP) in ATM (S49C, S707P, F858L, P1054R, and L1420F) in 26,101 breast cancer cases and 29,842 controls from 23 studies in the Breast Cancer Association Consortium. Results: Combining the data from all five SNPs, the odds ratio (OR) was 1.05 for being a heterozygote for any of the SNPs and 1.51 for being a rare homozygote for any of the SNPs with an overall trend OR of 1.06 (P-trend = 0.04). The trend OR among bilateral and familial cases was 1.12 (95% confidence interval, 1.02-1.23; P-trend = 0.02). Conclusions: In this large combined analysis, these five missense ATM SNPs were associated with a small increased risk of breast cancer, explaining an estimated 0.03% of the excess familial risk of breast cancer. Impact: Testing the combined effects of rare missense variants in known breast cancer genes in large collaborative studies should clarify their overall contribution to breast cancer susceptibility. Cancer Epidemiol Biomarkers Prev; 19(9); 2143-51. (C) 2010 AACR.